In light of the failure of Xu 2001 to disclose the claimed cyclodextrin or cyclodextrin derivatives, the rejection turns to Habon to make up for that deficiency. However, the Applicants respectfully submit that irrespective of the disclosure of cyclodextrin in Habon, one skilled in the art would have no reasonable expectation of success in making the combination. Prior to discussing the combination of Habon with Xu 2001, the Applicants will provide some background comments with respect to Xu 2001.

Xu 2001 discloses the effects of *dl*-, *l*- and *d*-3-n-butylphthalide (NBP) on platelet aggregation and thrombus formation. However, Xu 2001 is silent on formulation of dosages of butylphthalide, especially the inclusion complex of butylphthalide with cyclodextrin or cyclodextrin derivatives. In the animal assays of Xu 2001, almost pure butylphthalide (with a purity of more than 96%, 99.0% and 97.0%, line 18-19, col. 1) is administrated to rats or rabbits. The Applicants respectfully submit that the nearly pure utilization of butylphthalide is important, particularly when taken in the context of the results achieved by such use. In particular, Xu 2001 found that selected ones of the butylphthalides were apparently not effective in their inhibitory effects. For example, Xu 2001 discloses that "all of them showed no effect on thrombin-induced platelet aggregation." Of particular importance is the disclosure that "only high concentration [sic] of 1-NBP was found to decrease platelet TXA2 level." Thus, the Applicants respectfully submit that one skilled in the art would understand from Xu 2001 that butylphthalide is only sometimes effective, but is effective when administered as essentially pure active agent.

With that background in mind, we can now turn to Habon. Habon discloses the simulation of pharmacokinetic behavior of drug-cyclodextrin complexes. In the abstract, Habon discloses that complexation with cyclodextrin decreases the hydrophobicity of poorly soluble drugs and results in enhanced dissolution rates and higher solubility and in vivo experiments showed that this "molecular encapsulation" of drugs leads to enhanced bioavailability which is controlled by the solubilities, stability constants of the complexes, the molar ratio of drug: cyclodextrin, etc.

However, Habon does not provide useful teachings to one skilled in the art which drugs would be successfully complexed with cyclodextrin to improve the solubilities and, thus, bioavailability. Habon only mentions "poorly soluble drugs" and does not mention any specific drugs or compounds to be complexed with cyclodextrin throughout the entire text. Habon is theory and is completely silent with respect to butylphthalide. In view of the complete failure of Habon to

mention even a single active agent, it is singularly ineffective to provide one skilled in the art of a reasonable expectation that if the Habon disclosure were to be combined with the Xu 2001 disclosure, there would be a successful result.

Habon is theoretical and completely ignores the fact that it would be impossible for all drugs with different molecular structures, sizes or molecular weights in properties to be successfully complexed with cyclodextrin to improve solubilities or any other characteristics. Moreover, it must be remembered that the Applicants maintain the molar ratio of butylphthalide to cyclodextrin at a ratio of 1:1-10. In other words, the active agent is at most at about a 50% ratio relative to the cyclodextrin. This is sharply contrasted to the Xu 2001 disclosure which employs substantially pure butylphthalide. Given that Xu 2001 established that it was in many instances unsuccessful in showing activity, but in any event showed successful activity at near pure levels, the Applicants respectfully submit that one skilled in the art would not reasonably expect an inclusion complex of butylphthalide with cyclodextrin or cyclodextrin derivatives at a molar ratio of no more that about 50% butylphthalide to be effective. In fact, the Applicants respectfully submit that one skilled in the art would have a reasonable expectation that it would not be successful because of the prior demonstration by Xu 2001 that nearly pure butylphthalide is needed to have some expectation of success.

It should be remembered in evaluating patentability that there must be a motivation or a reason to make a combination of references or a modification of a single reference coupled with a reasonable expectation of success. The Applicants respectfully submit that irrespective of the presence of any hypothetical motivation to make a combination of Habon with Xu 2001, one skilled in the art would have no reasonable expectation of success in view of the teaching of Xu 2001 wherein success was only found at near pure administration levels. In any event, the Applicants do not claim that. Instead, the Applicants claim a maximum molar ratio of butylphthalide of about 50% relative to the cyclodextrin or cyclodextrin derivatives. Withdrawal of the rejection is accordingly respectfully requested.

Claims 6-11 stand rejected under 35 U.S.C. §103 over the hypothetical combination of Xu 2001 with Habon. The Applicants again note with appreciation the Examiner's detailed comments hypothetically applying the combination against those claims. The Applicants nonetheless

respectfully submit that the combination fails to result in what the Applicants claim. Details are set forth below.

The Applicants' Claim 6 includes three steps which are adding cyclodextrin or cyclodextrin derivatives into a solvent to obtain a solution with a concentration of 5-60%, adding butylphthalide to the solution, and stirring the resulting solution to obtain a liquid inclusion complex. The Applicants respectfully submit that the combination of Xu 2001 with Habon does not result in that claimed subject matter.

Xu 2001 does not disclose cyclodextrin and, accordingly, inherently does not disclose the first step of adding cyclodextrin or cyclodextrin derivatives into a solvent to obtain a solution with a concentration of 5-60%. This is important. Habon on the other hand discloses cyclodextrin and at least water as a solvent. However, there is also no disclosure of the Applicants' claimed subject matter of adding cyclodextrin or cyclodextrin derivatives into a solvent to obtain a solution with a concentration of 50-60%. This is also important because it means that the hypothetical combination of Xu 2001 with Habon would still result in a process for preparing a complex that does not include the step of adding cyclodextrin or cyclodextrin derivatives into a solvent vehicle to obtain a solution of a concentration of 5-60%.

Instead, Habon completely ignores the concentration of cyclodextrin or cyclodextrin derivatives in the solvent. There is no disclosure on this point at all. There is some minor disclosure of the molar ratios of a drug (although none are specifically identified) to cyclodextrin, there is no mention of the cyclodextrin concentration relative to the solvent. For example, there is a drug/cyclodextrin molar ratio of 1:1 on page 831, right-hand column, mid paragraph and a drug to cyclodextrin molar ratio of 1:2 on the same page at the bottom of the paragraph. However, there is no disclosure of the concentration of cyclodextrin or cyclodextrin derivatives with respect to the solvent. Therefore, the Applicants respectfully submit that even if one skilled in the art were to make the hypothetical combination, the result of that combination would still be different from what the Applicants claim. In fact, the Applicants respectfully submit that both of Habon and Xu 2001 are non-enabling as prior art with respect to Claims 6-11 in view of this complete deficiency of disclosure. Withdrawal of the rejection is respectfully requested.

Claim 15 stands rejected under 35 U.S.C. §103 over the hypothetical combination of Habon with Xu 1999. The Applicants again note with appreciation the Examiner's detailed comments

hypothetically applying the combination against Claim 15. However, the Applicants respectfully submit that one skilled in the art would have no reasonable expectation that the combination would be successful. The reasons are quite similar to the reasons set forth above with respect to the hypothetical combination of Habon with Xu 2001. Details are set forth below.

Xu 1999 discloses the effects of 3-n-butylphthalide on pial arterioles in focal-cerebral ischemia rats. Like Xu 2001, Xu 1999 is also completely silent with respect to formulation or dosages of butylphthalide and there is a complete failure to disclose cyclodextrin or an inclusion complex including cyclodextrin and butylphthalide.

Importantly, there is also a disclosure in Xu 1999 that nearly pure 3-n-butylphthalide with a purity of more than 96% was used. Thus, like Xu 2001, one skilled in the art would not have reasonable expectation of success that the combination of Habon with Xu 1999 would result in a successful method of treating ischemia-induced disease. The reason is that Xu 1999 uses nearly pure butylphthalide and the Applicants' Claim 15 uses an inclusion complex wherein the molar ratio butylphthalide to cyclodextrin or cyclodextrin derivatives is at most about 50% butylphthalide. As a result, one skilled in the art would have no expectation with respect to utilization of the claimed inclusion complex in a method of treating an ischemia-induced disease.

The Applicants again note that the prior art must not only provide reasons for modifying a primary reference, but must also provide a reasonable expectation of success. The Applicants have again demonstrated that there is no such reasonable expectation of success. In fact, the Applicants have demonstrated that there would be a reasonable expectation of a lack of success based not only on the Xu 1999 disclosure, but also on the Xu 2001 disclosure, irrespective of a hypothetical combination with Habon. Withdrawal of the rejection is respectfully requested.

In light of the foregoing, the Applicants respectfully submit that the entire Application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,

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